Physical Activity and Lower Limb Lymphedema among Uterine Cancer Survivors

JUSTIN C. BROWN[1], GABRIELLA M. JOHN[2], SAYA SEGAL[3], CHRISTINA S. CHU[4], and KATHRYN H. SCHMITZ[1]

[1]Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania, Philadelphia, PA; [2]Department of Epidemiology, Columbia University, New York, NY; [3]Division of Female Pelvic Medicine and Reconstructive Surgery, Robert Wood Johnson Medical School, Rutgers University, New Brunswick, NJ; and [4]Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, University of Pennsylvania, Philadelphia, PA

ABSTRACT

BROWN, J. C., G. M. JOHN, S. SEGAL, C. S. CHU, and K. H. SCHMITZ. Physical Activity and Lower Limb Lymphedema among Uterine Cancer Survivors. *Med. Sci. Sports Exerc.*, Vol. 45, No. 11, pp. 2091–2097, 2013. **Purpose**: Physical activity (PA) is known to provide physical and mental health benefits to uterine cancer survivors. However, it is unknown if PA is associated with lower limb lymphedema (LLL), an accumulation of protein-rich fluid in the lower limbs. Therefore, we sought to examine the association between PA and LLL in uterine cancer survivors, with a focus on walking. **Methods**: We conducted a cross-sectional study using mailed surveys among uterine cancer survivors who received care at a university-based cancer center. We asked about PA, walking, and LLL symptoms using validated self-report questionnaires. PA was calculated using MET-hours per week, and walking was calculated using blocks per day. **Results**: The response rate to our survey was 43%. Among the 213 uterine cancer survivors in our survey, 36% were classified as having LLL. Compared with participants who reported <3 MET·h·wk^{-1} of PA, participants who reported ≥ 18.0 MET·h·wk^{-1} of PA had an odds ratio of LLL of 0.32 (95% confidence interval, 0.15–0.69; $P_{trend} = 0.003$). Stratified analyses suggested the association between PA and LLL existed only among women with body mass index (BMI) <30 kg·m^{-2} ($P_{trend} = 0.007$) compared with women with BMI ≥ 30 kg·m^{-2} ($P_{trend} = 0.47$). Compared with participants who reported <4.0 blocks per day of walking, participants who reported ≥ 12 blocks per day of walking had an odds ratio of LLL of 0.19 (95% confidence interval, 0.09–0.43; $P_{trend} < 0.0001$). Stratified analyses suggested the association between walking and LLL was similar among women with BMI <30 kg·m^{-2} ($P_{trend} = 0.007$) and women with BMI ≥ 30 kg·m^{-2} ($P_{trend} = 0.03$). **Conclusion**: Participation in higher levels of PA or walking is associated with reduced proportions of LLL in dose–response fashion. These findings should be interpreted as preliminary and should be investigated in future studies. **Key Words**: GYNECOLOGIC CANCER, EXERCISE, MOBILITY DISABILITY, EDEMA, QUALITY OF LIFE

Lower limb lymphedema (LLL) affects 7%–47% of the 40,000 women diagnosed with uterine cancer each year in the United States (15,22). The prevalence of LLL varies depending on the modality and threshold used for diagnosis (8,9,41). LLL is characterized by swelling and accumulation of protein-rich fluid in the lower limbs (23,27), which impairs physical function (16) and reduces quality of life (5,14). LLL imparts long-term psychological burden due to limited efficacious therapies for symptom management (28,43). Established risk factors for the development of LLL include treatment with adjuvant radiation therapy, removal of ≥ 31 lymph nodes, and dissection of the saphenous vein (9,44,46). The incidence of

LLL will likely rise because the number of lymph nodes sampled among gynecologic cancer survivors has increased by as much as 350% in the past two decades (1). Therefore, efficacious interventions are needed to minimize the deleterious sequelae associated with LLL.

The American Cancer Society (35) suggests all uterine cancer survivors participate in physical activity (PA), following the guidelines set forth by the American College of Sports Medicine (ACSM) (38). However, LLL is associated with impaired leg blood flow (7), poor tissue oxygenation (42), and poor wound healing (13), such that the ACSM recommended uterine cancer survivors (or any gynecologic cancer survivor) with swelling or inflammation of the lower limbs be examined by a medical professional for clearance before engaging in PA (38). PA such as aerobic treadmill walking improves leg blood flow (19), tissue oxygenation (20,30), and wound healing (40) among people with peripheral artery disease (PAD) and venous leg ulcers. Furthermore, PA has been shown to improve symptoms of the lower limbs known to impair quality of life (31). These symptoms are similar to those associated with LLL experienced by cancer survivors.

It is unknown if PA associates with LLL among uterine cancer survivors. Identifying an association between PA and

LLL would provide a foundation for future research to examine the efficacy of PA in reducing LLL symptom frequency and severity among this group of cancer survivors. Alternatively, an association between PA and LLL may serve to identify cancer survivors whose symptoms preclude them from safely completing the standard prescription of PA for cancer survivors (38) and may require a tailored PA prescription to maximize the potential health benefits gained through PA participation. Therefore, the primary goal of our study was to examine the association between PA and LLL.

METHODS

Participants and procedures. We conducted a cross-sectional survey of patients with uterine cancer who received care at the Abramson Cancer Center at the University of Pennsylvania (Philadelphia, PA). Potential participants included women ≥20 yr old with histories of uterine cancer. Potentially eligible participants were identified using fellow surgical case logs from 2008 to 2010 and *International Classification of Diseases, Ninth Revision* (ICD-9), diagnosis codes 179.0 and 182.0–182.8 from 2006 to 2010. ICD-9 codes 179.0 and 182.0–182.8 are the primary codes used to classify cancers of the uterus. ICD-9 codes are commonly used in medical settings to systematically classify diagnoses for billing purposes. Participants identified by study staff as meeting inclusion criteria were sent a letter signed by their oncologist explaining the purpose of the study. Potentially eligible participants were provided with the option to decline participation within 2 wk of receiving the letter from their oncologist. Those who did not decline participation were sent a survey to complete. After 2 wk, a second survey was sent to those who did not reply to the first mailed survey (25). This protocol was approved by the University of Pennsylvania Institutional Review Board and the University of Pennsylvania Cancer Center. We classified women who provided their informed consent as those who mailed back a completed survey.

LLL assessment. The Gynecologic Cancer Lymphedema Questionnaire (GCLQ) was used to assess symptoms associated with LLL (10). The GCLQ is a validated self-report measure that assesses seven domains of symptoms in both lower extremities. The seven domains include heaviness, general swelling, limb-related swelling, infection, aching, numbness, and physical function, with one or more symptom questions per domain. Participants reporting five or more symptoms of the lower extremities within the seven previously listed domains were classified as having LLL. The GCLQ demonstrates good psychometric characteristics, with five or more symptoms maximizing the sensitivity, specificity, and positive and negative predictive values compared with other cutoff scores (10). Our study group omitted one of the three questions in the "general swelling" domain (question 20). In the validation study of the GCLQ, there were no women who reported only having answered "yes" to the question we omitted (personal communication

with J. Carter). We conducted sensitivity analyses assuming everyone responded "no" or "yes" to this question; our findings were consistent in all analyses with those reported herein.

PA assessment. The Paffenbarger Physical Activity Questionnaire was used to assess participation in PA (34). The Paffenbarger Physical Activity Questionnaire has been validated (3,26) and used previously among cancer survivors (32,33).

Participants were asked to "list any sports, leisure, or recreation activities you have participated in on a regular basis during the past year." Participants were also asked to list the average number of sessions per week and the duration of each session for each PA listed. Trained research staff then coded each PA listed with a MET using the compendium of PA (2). For reference, 1 MET is the energy expended when sitting quietly for 1 h, and 3.5 METs is walking for pleasure. For each MET value, we calculated the weekly activity-specific MET-hours per week as the product of the MET value, the number of sessions per week, and the number of hours per session. For each participant, we summed the activity-specific MET-hours per week to generate an aggregate measure of MET-hours per week. We created categories of MET-hours per week, defined as <3.0, 3.0–8.9, 9.0–17.9, and ≥18.0 that correspond to <1.0, 1.0–2.9, 3.0–5.9, and ≥6.0 $h \cdot wk^{-1}$ of moderate-intensity PA, consistent with prior analyses among cancer survivors (32,33).

Participants were asked "how many city blocks or their equivalent have you walked on an average day during the past year." It was noted on the questionnaire that "12 blocks equals one mile." We then created categories of blocks per day of walking, defined as <4.0, 4.0–11.9, and ≥12 blocks per day, which correspond to <0.25, 0.25 to <1, and ≥1 mile of walking per day, consistent with prior analyses among older adults (18).

Covariates. Information on covariates came from self-report or electronic medical records. Variables collected from self-report included age, marital status, race, education, employment, and body mass index (BMI). We used the Charlson comorbidity index (11,12) to identify comorbidities whose symptoms may be similar to LLL, such as congestive heart failure, PAD, and diabetes mellitus (45). We used the Gynecologic Oncology Group neurotoxicity sensory index to assess neuropathy from cancer treatment because neuropathy may influence participation in PA (21). This self-administered questionnaire quantifies numbness and discomfort in the hands and feet, and ranges from 0 to 16, with higher scores representing more severe neuropathy. Variables collected from the electronic medical record included pathology type, stage of cancer, time since diagnosis, and cancer treatment history.

Statistical analysis. Response rates to our survey were calculated using the method described by the American Association for Public Opinion Research (25). We performed descriptive statistics and bivariate analyses on all study variables using the Wilcoxon rank-sum test for continuous

TABLE 1. Demographic characteristics stratified by LLL status.

Variable	Total Sample (n = 213)	LLL (n = 77)	No LLL (n = 136)	P^a
Age (yr)	63.6 ± 10.6	62.7 ± 10.2	64.0 ± 10.9	0.24
Marital status, no. (%)				0.54
Never married	20 (9%)	8 (10%)	12 (9%)	
Married	128 (60%)	47 (61%)	81 (60%)	
Divorced or separated	31 (15%)	8 (10%)	23 (17%)	
Widowed	33 (16%)	14 (18%)	19 (14%)	
Self-reported race, no. (%)				0.66
White	177 (84%)	66 (86%)	111 (82%)	
Black	28 (13%)	8 (10%)	20 (15%)	
Other	7 (3%)	3 (4%)	4 (3%)	
Education, no. (%)				0.15
High school or less	46 (22%)	16 (21%)	30 (22%)	
Some college	51 (24%)	13 (17%)	38 (28%)	
College degree or more	114 (54%)	47 (62%)	67 (50%)	
Employment, no. (%)				0.61
Retired	94 (45%)	35 (46%)	59 (44%)	
Unemployed	7 (3%)	4 (5%)	3 (2%)	
Homemaker	16 (8%)	6 (8%)	10 (7%)	
Other	14 (7%)	3 (4%)	11 (8%)	
Full time	80 (38%)	28 (37%)	52 (38%)	

[a]By Wilcoxon rank-sum test or Fisher exact test. Values may not sum up to 213 or 100% because of rounding error and item nonresponse.

variables and Fisher exact test for categorical variables. We used logistic regression models to estimate the odds ratio (OR) of reporting LLL with 95% confidence intervals (CI). The P value for the linear trend test across categories (P_{trend}) was calculated using the median value for each category as a continuous variable in a logistic regression model. We examined unadjusted regression models, then adjusted for age and BMI, and subsequently built a multivariable regression model, adjusting for demographic and clinical characteristics. Variables analyzed as potential covariates are shown in Tables 1 and 2. Statistical tests were two sided, and $P < 0.05$ was the threshold for statistical significance. All statistical analyses were conducted using Stata 12 (StataCorp, College Station, TX).

RESULTS

Mailed survey results. We identified 531 potentially eligible participants using the fellow surgical case logs and ICD-9 codes. Among the 531 mailed letters, we had a 43% response rate. Sixty-seven potentially eligible participants were not interested in participating in our study, and 213 potentially eligible participants did not respond to either the letter or the mailed survey. There were 19 letters returned by the post office, labeled as undeliverable, and an additional seven people had died. A total of 225 participants returned the surveys, and 12 were subsequently identified as not meeting inclusion criteria (i.e., 10 diagnosed with cancer before 2006 and two misclassified (diagnosed with other gynecologic cancers)). The remaining 213 eligible participants replied to our survey and contributed data to the study analyses.

Participant characteristics. Demographic characteristics of the study participants are depicted in Table 1. The age of the 213 participants ranged from 29 to 94 yr. The majority of participants reported being white, married, high

school graduates, and retired or working full time. Clinical characteristics of the study participants are depicted in Table 2. Participants were commonly diagnosed with stage I endometrioid adenocarcinoma and treated with surgery. The BMI of study participants ranged from 14 to 67 kg·m^{-2}. The neuropathy impairment index indicated that the women had minimal symptoms in their hands and feet. A small proportion of the study participants were previously diagnosed with conditions that may clinically resemble LLL symptoms, including congestive heart failure (4%), PAD (2%), and diabetes mellitus (14%). These prior comorbidities were not associated with LLL symptom classification ($P > 0.05$).

Characteristics between participants with versus without LLL. Among the 213 participants, 77 (36%) reported five or more symptoms on the GCLQ and were classified as having LLL. There existed no significant difference in demographic and clinical characteristics between women classified as having LLL versus not having LLL.

LLL symptoms by level of PA and walking distance. Among the 213 study participants, 40%, 13%, 13%, and 35% reported participating in <3.0, 3.0–8.9, 9.0–17.9, and ≥18.0 MET·h·wk^{-1} of PA, respectively (Table 3). The

TABLE 2. Clinical characteristics stratified by LLL status.

Variable	Total Sample (n = 213)	LLL (n = 77)	No LLL (n = 136)	P^a
Pathology type, no. (%)				0.73
Endometrioid adenocarcinoma	158 (75%)	57 (74%)	101 (75%)	
Papillary serous or clear cell	35 (17%)	14 (18%)	21 (16%)	
Sarcoma	8 (4%)	2 (3%)	6 (4%)	
Carcinosarcoma	8 (4%)	2 (3%)	6 (4%)	
Other (undifferentiated)	3 (1%)	2 (3%)	1 (1%)	
Stage, no. (%)				0.76
1	157 (74%)	57 (74%)	100 (74%)	
2	13 (6%)	5 (6%)	8 (6%)	
3	26 (12%)	9 (12%)	17 (13%)	
4	5 (2%)	3 (4%)	2 (1%)	
Unknown	12 (6%)	3 (4%)	9 (7%)	
Treatment modalities, no. (%)				0.51
Surgery	100 (47%)	40 (52%)	60 (44%)	
Surgery, chemotherapy	37 (17%)	12 (16%)	25 (18%)	
Surgery, radiation	47 (22%)	13 (17%)	34 (25%)	
Surgery, chemotherapy, radiation	22 (10%)	10 (13%)	12 (9%)	
None or unknown	7 (3%)	2 (3%)	5 (4%)	
No. of nodes removed	8.9 ± 10.2	7.6 ± 9.8	9.7 ± 10.4	0.10
Neuropathy impairment index[b]	3.3 ± 3.6	2.8 ± 3.4	3.6 ± 3.7	0.17
Time since diagnosis, no. (%)				0.74
0–2 yr	69 (32%)	23 (30%)	46 (34%)	
3–4 yr	94 (44%)	34 (44%)	60 (44%)	
5–6 yr	50 (23%)	20 (26%)	30 (22%)	
BMI (kg·m^{-2})	31.1 ± 8.9	30.8 ± 9.3	31.2 ± 8.7	0.66
Prior comorbidities[c], no. (%)				
Congestive heart failure	8 (4%)	2 (3%)	6 (5%)	0.50
PAD	5 (2%)	3 (4%)	2 (2%)	0.27
Diabetes mellitus	29 (14%)	11 (15%)	18 (14%)	0.82

[a]By Wilcoxon rank-sum test or Fisher exact test. Values may not sum up to 213 or 100% because of rounding error and item nonresponse.
[b]The neuropathy impairment index is scored from 0 to 16, with higher scores representing more severe neuropathy in the hands and feet.
[c]Comorbidities associated with symptoms in the lower limbs that may resemble LLL.

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TABLE 3. Cases of LLL by level of PA, walking distance, and BMI.

PA (MET·h·wk^{-1})	Total in Category	Cases of LLL	Model 1[a] OR (95% CI)	Model 2[b] OR (95% CI)	Model 3[c] OR (95% CI)
<3.0	85	39 (46%)	1.0, referent	1.0, referent	1.0, referent
3.0–8.9	27	12 (44%)	0.94 (0.40–2.25)	0.92 (0.37–2.28)	0.75 (0.28–1.99)
9.0–17.9	27	9 (33%)	0.59 (0.24–1.46)	0.31 (0.24–1.52)	0.50 (0.17–1.45)
≥18.0	74	17 (23%)	0.35 (0.18–0.70)	0.36 (0.18–0.73)	0.32 (0.15–0.69)
P_{trend}	—	—	0.002	0.004	0.003
Walking (blocks per day)	**Total in Category**	**Cases of LLL**	**Model 1[a] OR (95% CI)**	**Model 2[b] OR (95% CI)**	**Model 3[c] OR (95% CI)**
<4.0	75	41 (55%)	1.0, referent	1.0, referent	1.0, referent
4.0–11.9	53	15 (28%)	0.33 (0.15–0.69)	0.31 (0.14–0.68)	0.24 (0.10–0.57)
≥12.0	78	18 (23%)	0.25 (0.12–0.50)	0.23 (0.11–0.48)	0.19 (0.09–0.43)
P_{trend}	—	—	<0.0001	<0.0001	<0.0001
BMI (kg·m^{-2})	**Total in Category**	**Cases of LLL**	**Model 1[a] OR (95% CI)**	**Model 2[b,d] OR (95% CI)**	**Model 3[c,d] OR (95% CI)**
<25.0	56	20 (36%)	1.0, referent	1.0, referent	1.0, referent
25.0–29.9	47	17 (36%)	1.02 (0.45–2.29)	1.01 (0.45–2.27)	1.38 (0.55–3.44)
≥30.0	110	40 (36%)	1.03 (0.53–2.01)	1.01 (0.52–1.98)	1.12 (0.52–2.43)
P_{trend}	—	—	0.94	0.97	0.85

[a]Model 1 is the crude (unadjusted) OR and 95% CI.
[b]Model 2 is the age- and BMI-adjusted OR and 95% CI.
[c]Model 3 is the fully adjusted (multivariable) OR and 95% CI, controlling for age, BMI, race, cancer stage, type of treatment received, years since diagnosis, and diabetes.
[d]BMI excluded as a covariate in these analyses.

odds of LLL decreased as MET-hours per week of PA increased (P_{trend} = 0.003). Compared with participants who reported <3 MET·h·wk^{-1} of PA, participants who reported ≥18.0 MET·h·wk^{-1} of PA had an OR of 0.32 (95% CI, 0.15–0.69). The most common PA reported were walking (42%), aerobic gym-based activities including the recumbent bicycle and elliptical machine (11%), and swimming (8%).

Among the 213 study participants, 36%, 26%, and 38% reported walking <4.0, 4.0–11.9, and ≥12 blocks per day, respectively (Table 3). The odds of LLL decreased as the blocks per day of walking increased (P_{trend} < 0.0001). Compared with participants who reported <4.0 blocks per day of walking, participants who reported ≥12 blocks per day of walking had a multivariable-adjusted OR of 0.19 (95% CI, 0.09–0.43).

Among the 213 study participants, 26%, 22%, and 52% reported a BMI of <25.0, 25.0–29.9, and ≥30.0 kg·m^{-2}, respectively (Table 3). The odds of LLL did not change as BMI increased (P_{trend} = 0.85).

We also assessed the joint effects of BMI with PA and BMI with walking (Table 4). Although the interaction between BMI and PA was not statistically significant ($P_{interaction}$ = 0.27), stratified analyses suggested the association between PA and LLL existed only among women with BMI <30 kg·m^{-2} (P_{trend} = 0.007) compared with women with BMI ≥30 kg·m^{-2} (P_{trend} = 0.47). The interaction between BMI and walking was not statistically significant ($P_{interaction}$ = 0.56), and stratified analyses suggested the association between walking and LLL was similar among women with BMI <30 kg·m^{-2} (P_{trend} = 0.007) compared with women with BMI ≥30 kg·m^{-2} (P_{trend} = 0.03).

DISCUSSION

The major findings of this study are that 36% of uterine cancer survivors in our sample have LLL on the basis of symptom self-report, and uterine cancer survivors who participate in more PA and walking are less likely to report

symptoms sufficient for a diagnosis of LLL. These findings, particularly PA participation, were more pronounced among women with BMI <30 kg·m^{-2}. BMI was not independently associated with LLL. Our data now provide evidence linking PA, walking, and LLL. Among uterine cancer survivors who engage in the highest level of PA or walking, there were 68% and 81% reduced odds of reporting LLL compared with uterine cancer survivors who engage in the lowest levels of PA or walking, respectively.

Although these findings are promising, they should be interpreted as preliminary. The major limitation of this study is the cross-sectional design, in which it is impossible to determine the direction of any causal association. It is plausible that uterine cancer survivors who engage in more PA or walking subsequently experience fewer LLL-related symptoms. Conversely, it is plausible that uterine cancer survivors with more severe LLL symptoms may be physically or psychologically unable to engage in PA or walking. BMI in our study was self-reported, which may be subject to bias. However, BMI is highly correlated with objective measures of height and weight and is appropriate for epidemiologic studies (29). PA in our study was self-reported. Although self-reported PA is valid and correlated with objective measures of PA (47), 47% of participants in our study reported

TABLE 4. Multivariable-adjusted cases of LLL by level of PA and walking distance, stratified by BMI[a].

	BMI <30 kg·m^{-2} (n = 103)	BMI ≥30 kg·m^{-2} (n = 110)	$P_{interaction}$
PA (MET·h·wk^{-1})			
<3.0	1.0, referent	1.0, referent	0.27
3.0–8.9	1.01 (0.20–5.10)	0.65 (0.16–2.70)	
9.0–17.9	0.24 (0.03–1.66)	0.84 (0.19–3.64)	
≥18.0	0.21 (0.06–0.70)	0.63 (0.21–1.92)	
P_{trend}	0.007	0.47	
Walking (blocks per day)			
<4.0	1.0, referent	1.0, referent	0.56
4.0–11.9	0.20 (0.05–0.87)	0.26 (0.08–0.90)	
≥12.0	0.15 (0.04–0.61)	0.27 (0.09–0.83)	
P_{trend}	0.007	0.03	

[a]Fully adjusted (multivariable) OR and 95% CI, controlling for age, race, cancer stage, type of treatment received, years since diagnosis, and diabetes.

meeting PA guidelines (i.e., ≥9.0 MET·h·wk^{-1}), whereas only approximately 10% of US adults meet such guidelines (48). Therefore, it is plausible that participants in our study may have over-reported their PA, consistent with the hypothesis that uterine cancer survivors are less physically active and have higher BMI. Another limitation of our study was the omission of question 20 in the "general swelling" domain of the GCLQ survey. The current gold standard method to diagnose LLL is the circumferential measures of the lower limbs and a clinical examination. However, this method has not been adopted for use in routine clinical care (8). Our method to assess LLL relied on symptoms determined using a self-report questionnaire that was validated against circumferential measures of the lower limbs and had excellent psychometric characteristics (10).

The optimal exercise modality to reduce LLL symptom burden is unknown. This is a result of a limited understanding of the physiologic complexities of LLL. People with PAD use treadmill walking as a rehabilitative modality to improve leg claudication symptoms (17). Resistance training has also been recommended as a useful adjunct to treadmill walking for people with PAD (31). Among 156 people with PAD who were randomized to 24 wk of aerobic treadmill walking, lower extremity resistance training, or control, people in the aerobic treadmill walking group had significantly improved 6-min walking distance times and improved time to onset of leg symptoms compared with those in the control group (31). The weightlifting group had improved quality of life and stair climbing ability compared with the control group (31). The three-arm design such as that described previously may be the most efficient approach to test the safety and efficacy of various exercise modalities among uterine cancer survivors with LLL.

Recent evidence has emerged that weightlifting exercise is a safe and efficacious modality for upper extremity lymphedema among breast cancer survivors (36,39). Among breast cancer survivors with upper extremity lymphedema, weightlifting resulted in a 50% risk reduction of lymphedema exacerbations requiring medical treatment and a significant reduction in the severity of self-reported lymphedema symptoms over 1 yr (36). Despite physiologic differences between upper extremity lymphedema and LLL, a hypothesis would be to examine the use of weightlifting among cancer survivors with LLL. A small pilot study of weightlifting has been conducted among 10 cancer survivors with LLL (24). After 5 months of weightlifting, participants had improvements in muscular strength and physical functioning ($P < 0.05$) compared with baseline values. There were no significant changes in objective LLL leg volume when measured using perometry. Two of the 10 participants developed cellulitis, a bacterial infection requiring broad-spectrum antibiotics during the study. Therefore, the safety and efficacy of weightlifting among cancer survivors with LLL remains to be elucidated (24).

Daily voluntary walking has been demonstrated to correlate with the distance women can walk without difficulty (6).

Furthermore, a program that increases voluntary walking may have implications for disability, mortality, and health care costs (18). Compared with those who could walk 0.25 mile without difficulty, those who had difficulty or were unable to walk 0.25 mile were at 1.57- or 2.73-fold higher risk for mortality among 5895 community-dwelling older adults, respectively. A dose–response relation between ability to walk 0.25 mile and medical care costs and hospitalizations has been observed: as ability to walk 0.25 mile decreases, medical care costs and hospitalizations may increase proportionally (18). Therefore, future intervention studies designed to improve functional mobility among uterine cancer survivors with LLL may provide a multitude of benefits, including reduced disability, mortality, and health care costs. To this end, randomized controlled trials designed to reduce disability among uterine cancer survivors with LLL should consider these outcomes as being important on patient and policy levels (4).

As noted in the introduction, if LLL precludes women participating in the recommended levels of PA (i.e., if reverse causality exists), then our findings have clinical implications. For example, it is important for clinicians to know that the ACSM guidelines for exercise among cancer survivors (38) may need to be tailored to allow women with LLL to engage in PA that is safe, feasible, and efficacious to promote their physical and mental health. Future cohort studies that measure PA after diagnosis and follow participants longitudinally until incident LLL diagnosis would help to delineate the temporal relation of PA with LLL. In the absence of reverse causality, PA may be an intervention to prevent LLL among those at risk of developing LLL and to reduce symptom burden among those with LLL. The potential utility of PA across the LLL spectrum—from prevention to treatment—is consistent with other forms of lymphedema such as upper extremity lymphedema among breast cancer survivors. For example, weightlifting reduces the risk of incident upper extremity lymphedema by 36% among those at risk of developing upper extremity lymphedema (37) and reduces the need for complete decongestive treatment by 53% among those with upper extremity lymphedema (36). Our hypothesis is that PA would have similar effects on LLL like that of upper extremity lymphedema. The remaining questions to be answered include 1) the temporal sequence of PA and incident LLL, 2) the efficacy and safety of PA to prevent and/or treat LLL, and 3) the type of PA modality (i.e., aerobic, resistance, and neuromuscular) that should be prescribed to maximize LLL outcomes and promote the health and longevity of uterine cancer survivors.

CONCLUSION

Among uterine cancer survivors, approximately 36% have LLL, determined using a validated symptom self-report (10). Participation in higher levels of PA or walking was associated with reduced proportions of LLL in dose–response

fashion, such that the group who engaged in the highest levels of PA or walking reported the smallest proportion of LLL cases. These findings should be interpreted as preliminary and should be subject to investigation in future studies.

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